

CLAIMS

1. An isolated polypeptide for medical use, said polypeptide comprising an amino acid sequence selected from the group consisting of:
 - 5 a) the amino acid sequence selected from the group consisting of SEQ ID No. 3, 4, 5, 8, 9, 10, 13, 14, 15, 19, 20, 21, 22, 23, and 24;
 - b) a sequence variant of the amino acid sequence selected from the group consisting of SEQ ID No. 3, 4, 5, 8, 9, 10, 13, 14, 15, 19, 20, 21, 22, 23, and 24, wherein the variant has at least 70% sequence identity to said SEQ ID No.; and
 - 10 c) a biologically active fragment of at least 50 contiguous amino acids of any of a) through b).
2. The polypeptide of claim 1 that is a naturally occurring allelic variant of the sequence selected from the group consisting of SEQ ID No. 3, 4, 5, 8, 9, 10, 13, 14, 15, 19, 20,
15 21, 22, 23, and 24.
3. The polypeptide of claim 2, wherein the allelic variant comprises an amino acid sequence that is the translation of a nucleic acid sequence differing by a single nucleotide from a nucleic acid sequence selected from the group consisting of SEQ ID
20 No. 1, 2, 6, 7, 11, 12, 16, 17, and 18.
4. The polypeptide of claim 1 that is a variant polypeptide described therein, wherein any amino acid specified in the chosen sequence is changed to provide a conservative substitution.
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5. The polypeptide of claim 1, wherein the signal peptide has been replaced by a heterologous signal peptide.
6. The polypeptide of claim 1, having at least 70% sequence identity to a protein having a
30 sequence selected from the group consisting of SEQ ID No. 5, 10, and 15 more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 5, 10, and 15.
- 35 7. The polypeptide of claim 1, having at least 70% sequence identity to a protein having a sequence selected from the group consisting of SEQ ID No. 4, 9, and 14, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%,

more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 4, 9, and 14.

- 5 8. The polypeptide of claim 1, having at least 70% sequence identity to a protein having a sequence selected from the group consisting of SEQ ID No. 3, 8, and 13, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 3, 8, and 13.
- 10 9. The polypeptide of claim 1, having at least 70% sequence identity to a protein having a sequence selected from the group consisting of SEQ ID No. 19, 20, 21, 22, 23, and 24, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 19, 20, 21, 22, 23, and 24.
- 15 10. The polypeptide of claim 1, having at least 70% sequence identity to the protein having the sequence of SEQ ID No. 3, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 3.
- 20 11. The polypeptide of claim 1, having at least 70% sequence identity to the protein having the sequence of SEQ ID No. 4, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 4.
- 25 12. The polypeptide of claim 1, having at least 70% sequence identity to the protein having the sequence of SEQ ID No. 5, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 5.
- 30 13. The polypeptide of claim 1, having at least 70% sequence identity to the protein having the sequence of SEQ ID No. 19, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 19.
- 35 14. The polypeptide of claim 1, having at least 70% sequence identity to the protein having the sequence of SEQ ID No. 22, more preferably at least 75%, more preferably at least

80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 22.

15. The polypeptide of claim 1, wherein the fragment is selected from the group consisting of:

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- i) AA₃₀-AA₂₈₈ of SEQ ID No 3, and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₅-AA₂₉₃ of SEQ ID No 3;
- ii) AA₂₈-AA₂₈₆ of SEQ ID No 13 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₃-AA₂₉₁ of SEQ ID No 13;
- iii) AA₃₁-AA₂₈₉ of SEQ ID No 8 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₆-AA₂₉₄ of SEQ ID No 8; and
- iv) variants of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 20 of the amino acid residues in the sequence are so changed.

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16. The polypeptide of claim 1, selected from the group consisting of:

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- i) AA₁₇₁-AA₂₈₈ of SEQ ID No 3, and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₁₆₅-AA₂₈₈ of SEQ ID No 3;
- ii) AA₁₆₉-AA₂₈₆ of SEQ ID No 13 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₁₆₄-AA₂₉₁ of SEQ ID No 13;
- iii) AA₁₇₂-AA₂₈₉ of SEQ ID No 8 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, i.e. up to AA₁₆₇-AA₂₉₄ of SEQ ID No 8;
- iv) variants of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 10 of the amino acid residues in the sequence are so changed.

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17. The polypeptide of claim 1, wherein the fragment is selected from the group consisting of

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- i) AA₃₀-AA₁₁₈ of SEQ ID No 3, and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₅-AA₁₂₃ of SEQ ID No 3;

- ii) AA₂₈-AA₁₁₆ of SEQ ID No 13 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₃-AA₁₂₁ of SEQ ID No 13;
- 5 iii) AA₃₁-AA₁₁₉ of SEQ ID No 8 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₆-AA₁₂₄ of SEQ ID No 8; and
- iv) variants of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 10 of the amino acid residues in the sequence are so changed.

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18. The polypeptide of any of the preceding claims 15 to 17, wherein the changed amino acids are selected from those designated as unconserved, weakly conserved or strongly conserved in Figure 3a.

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19. The polypeptide of any of the preceding claims, being capable of forming at least one intramolecular cystin bridge.

20. The polypeptide of any of the preceding claims, comprising a dimer of NsG33 linked through an intermolecular cystin bridge.

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21. The polypeptide according to any of the preceding claims, further comprising an affinity tag, such as a polyhis tag, a GST tag, a HA tag, a Flag tag, a C-myc tag, a HSV tag, a V5 tag, a maltose binding protein tag, a cellulose binding domain tag.

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22. An isolated nucleic acid molecule for medical use comprising a nucleic acid sequence encoding a polypeptide or its complementary sequence, said polypeptide comprising an amino acid sequence selected from the group consisting of:

- a) the amino acid sequence selected from the group consisting of SEQ ID No. 3, 4, 5, 8, 9, 10, 13, 14, 15, 19, 20, 21, 22, 23, and 24;
- 30 b) a sequence variant of the amino acid sequence selected from the group consisting of SEQ ID No. 3, 4, 5, 8, 9, 10, 13, 14, 15, 19, 20, 21, 22, 23, and 24, wherein the variant has at least 70% sequence identity to said SEQ ID No.; and
- c) a biologically active fragment of at least 50 contiguous amino acids of any of a) through b).

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23. The nucleic acid molecule of claim 22, wherein the nucleic acid molecule comprises the nucleotide sequence of a naturally occurring allelic nucleic acid variant.

24. The nucleic acid molecule of claim 22 that encodes a variant polypeptide, wherein the variant polypeptide has the polypeptide sequence of a naturally occurring polypeptide variant.

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25. The nucleic acid molecule of claim 22, wherein the nucleic acid molecule differs by a single nucleotide from a nucleic acid sequence selected from the group consisting of SEQ ID No. 1, 2, 6, 7, 11, 12, 16, 17, and 18.

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26. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to a sequence selected from the group consisting of SEQ ID No. 5, 10, and 15 more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 5, 10, and 15.

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27. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to a sequence selected from the group consisting of SEQ ID No. 4, 9, and 14, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 4, 9, and 14.

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28. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to a sequence selected from the group consisting of SEQ ID No. 3, 8, and 13, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 3, 8, and 13.

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29. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to a sequence selected from the group consisting of SEQ ID No. 19, 20, 21, 22, 23, and 24, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence selected from the group consisting of SEQ ID No. 19, 20, 21, 22, 23, and 24.

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30. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to SEQ ID No. 3, more preferably at least 75%, more preferably

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at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 3.

5 31. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to SEQ ID No. 4, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 4.

10 32. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to SEQ ID No. 5, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 5.

15 33. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to SEQ ID No. 19, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 19.

20 34. The nucleic acid molecule of claim 22, wherein the encoded polypeptide has at least 70% sequence identity to SEQ ID No. 22, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a protein having the sequence of SEQ ID No. 22.

25 35. The nucleic acid molecule of claim 22, wherein the nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of

- a) the nucleotide sequence selected from the group consisting of SEQ ID No. 1, 2, 6, 7, 11, 12, 16, 17, and 18;
- b) a nucleotide sequence having at least 70% sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID No. 1, 2, 6, 7, 11, 12, 16, 17, and 18;
- 30 c) a nucleic acid sequence of at least 150 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID No. 1, 2, 6, 7, 11, 12, 16, 17, and 18;
- c) the complement of a nucleic acid capable of hybridising with nucleic acid having the sequence selected from the group consisting of SEQ ID No.: 1, 2, 6, 7, 11, 12, 16, 17, and 18 under conditions of high stringency; and
- 35 d) the nucleic acid sequence of the complement of any of the above.

36. The nucleic acid molecule of claim 22, comprising a nucleotide sequence having at least 70% sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID No. 2, 7, 12, 16, 17, and 18, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 2, 7, 12, 16, 17, or 18.
37. The nucleic acid molecule of claim 22, comprising a nucleotide sequence having at least 70% sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID No. 16, 17, and 18, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 16, 17, or 18.
38. The nucleic acid molecule of claim 22, comprising a nucleotide sequence having at least 70% sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID No. 2 and 16, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 2 and 16.
39. The nucleic acid molecule of claim 22, having at least 70%, more preferably at least 75%, more preferably at least 80%, preferably at least 85%, more preferred at least 90%, more preferred at least 95%, more preferred at least 98% sequence identity to a polynucleotide sequence selected from the group consisting of nucleotides 187-996 of SEQ ID NO: 2, nucleotides 74-883 of SEQ ID No 7 and nucleotides 64-873 of SEQ ID No. 12.
40. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 1, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 1.
41. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 2, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 2.

42. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 6, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 6.
43. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 7, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 7.
44. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 11, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 11.
45. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 12, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 12.
46. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 16, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 16.
47. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 17, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 17.
48. The nucleic acid molecule of claim 22, having at least 70% sequence identity to the nucleic acid molecule having the sequence of SEQ ID No. 18, more preferably at least 75%, more preferably at least 80%, more preferably at least 95%, more preferably at least 98%, more preferably a nucleic acid having the sequence of SEQ ID No. 18.
49. The nucleic acid molecule of claim 22, being codon optimised for expression in *E. coli*, Chinese Hamster, Baby Hamster, Yeast, insect and/or fungus.

50. The nucleic acid molecule of claim 22, wherein the nucleic acid molecule is a shuffled variant between SEQ ID No 2, and 7 and/or 12.

5 51. A vector comprising the nucleic acid molecule of any of the preceding claims 22 to 50.

52. The vector of claim 51, further comprising a promoter operably linked to the nucleic acid molecule.

10 53. The vector of claim 52, wherein the promoter is selected from the group consisting of: CMV, human UbiC, JeT, RSV, Tet-regulatable promoter, Mo-MLV-LTR, Mx1, EF-1alpha.

15 54. The vector of claim 51 or 52, being selected from the group consisting of vectors derived from the Retroviridae family including lentivirus, HIV, SIV, FIV, EAV, CIV.

55. The vector of claim 51 or 52, being selected from the group consisting of alphavirus, adenovirus, adeno associated virus, baculovirus, HSV, coronavirus, Bovine papilloma virus, Mo-MLV, preferably adeno associated virus.

20 56. An isolated host cell transformed or transduced with the vector of any of the claims 51 to 55.

25 57. The host cell of claim 56, being selected from the group consisting of E. coli, Yeast, Saccharomyces cerevisiae, Aspergillus, Sf9 insect cells.

58. The host cell of claim 56, being selected from the group consisting of mammalian cells, such as human, feline, porcine, simian, canine, murine, rat, mouse and rabbit.

30 59. The host cell of claim 58, being selected from the group consisting of immortalised retinal pigmented epithelial cells, such as ARPE-19 cells, immortalised human fibroblasts, and immortalised human astrocytes.

60. The host cell of claim 59, being attached to a matrix.

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61. The host cell of claim 58, being selected from the group consisting of stem cells, including human neural stem or precursor cells, human glial stem or precursor cells, and foetal stem cells.

5 62. The host cell of claim 58, being selected from the group consisting of CHO, CHO-K1, HEI193T, HEK293, COS, PC12, HiB5, RN33b, BHK cells.

10 63. A packaging cell line capable of producing an infective virus particle, said virus particle comprising a Retroviridae derived genome comprising a 5' retroviral LTR, a tRNA binding site, a packaging signal, a promoter operably linked to a polynucleotide sequence encoding the polypeptide of any of the claims 1 to 21, an origin of second strand DNA synthesis, and a 3' retroviral LTR.

15 64. The packaging cell line of claim 62, wherein the genome is lentivirally derived and the LTRs are lentiviral.

65. An implantable biocompatible cell device, the device comprising:

- 20 i) a semipermeable membrane permitting the diffusion of a protein as defined by any of the preceding claims 1 to 21 and/or a virus vector; and
- ii) a composition of cells according to any of the claims 56 to 62 or a packaging cell line according to any of the claims 63 to 64.

66. The device of claim 65, wherein the semipermeable membrane is immunoisulatory.

25 67. The device of claim 65, wherein the semipermeable membrane is microporous.

68. The device of claim 65, wherein the device further comprises a matrix disposed within the semipermeable membrane.

30 69. The device of claim 65, wherein the device further comprises a tether anchor.

70. The device of claim 65, wherein said device comprises a core comprising living packaging cells that secrete a viral vector for infection of a target cell, wherein the viral vector is a retrovirus, the vector comprising a heterologous gene encoding a polypeptide according to any of claims 1 to 21, operably linked to a promoter that regulates the expression of said polypeptide in the target cell; and an external jacket surrounding said core, said jacket comprising a permeable biocompatible material, said

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material having a porosity selected to permit passage of retroviral vectors of approximately 100 nm diameter thereacross, permitting release of said viral vector from said capsule.

5 71. The device of claim 70, wherein the core additionally comprises a matrix, the packaging cells being immobilized by the matrix.

72. The device of claim 70, wherein the jacket comprises a hydrogel or thermoplastic material.

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73. A pharmaceutical composition comprising

- i) the polypeptide of any of the claims 1 to 21; or
 - ii) the isolated nucleic acid sequence of any of the claims 22 to 50; or
 - iii) the expression vector of any of the claims 51 to 55; or
 - 15 iv) a composition of host cells according to any of the claims 56 to 62; or
 - v) a packaging cell line according to any of the claims 63 to 64; or
 - vi) an implantable biocompatible cell device according to any of the claims 65 to 72; and
- a pharmaceutically acceptable carrier.

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74. The use of

- i) the polypeptide of any of the claims 1 to 21; or
 - ii) the isolated nucleic acid sequence of any of the claims 22 to 50; or
 - iii) the expression vector of any of the claims 51 to 55; or
 - 25 iv) a composition of host cells according to any of the claims 56 to 62;
 - v) an implantable biocompatible cell device according to any of the claims 65 to 72; or
 - vi) a packaging cell line according to any of the claims 63 to 64;
- for the manufacture of a medicament.

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75. The use of claim 74, wherein said medicament is for the treatment of an immunological disorder.

35 76. The use of claim 75, wherein the immunological disorder is selected from the group consisting of: infectious diseases, immune deficiencies, cancer, autoimmune disorders including multiple sclerosis, allergic reactions and conditions, and graft-versus-host disease.

77. The use of claim 74, wherein said medicament is for the treatment of a disease, disorder, or damage associated with the nervous system.

5 78. The use of claim 77, wherein said medicament is for the treatment of a disease, disorder, or damage involving injury to the brain, brain stem, the spinal cord, and/or peripheral nerves, including but not limited to conditions such as stroke, traumatic brain injury, spinal cord injury, diffuse axonal injury, epilepsy, neuropathy, peripheral neuropathy and associated pain and other symptoms.

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79. The use of claim 77, wherein the Nervous System disorder involves degeneration of neurons and their processes in the brain, brain stem, the spinal cord, and/or the peripheral nerves, including but not limited to Parkinson's Disease, Alzheimer's Disease, senile dementia, Huntington's Disease, amyotrophic lateral sclerosis, neuronal injury associated with multiple sclerosis, and associated symptoms.

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80. The use of claim 79, wherein the neurodegenerative disease is Parkinson' Disease.

81. The use of claim 79, wherein the neurodegenerative disease is Huntington's Disease.

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82. The use of claim 79, wherein the neurodegenerative disease is amyotrophic lateral sclerosis.

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83. The use of claim 77, wherein the nervous system disorder is a disease, disorder, or damage involving dysfunction and/or loss of neurons in the brain, brain stem, the spinal cord, and/or peripheral nerves, including but not limited to conditions caused by metabolic diseases, nutritinal deficiency, toxic injury, malignancy, and/or genetic or idiopathic conditions including but not limited to diabetes, renal dysfunction, alcoholism, chemotherapy, chemical agents, drug abuse, vitamin deficiency, and infection.

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84. The use of claim 83 or 78, wherein the disease is peripheral neuropathy and associated pain.

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85. The use of claim 77, wherein the nervous system disorder is a disease, disorder, or damage involving degeneration or sclerosis of glia such as oligodendrocytes, astrocytes and Schwann cells in the brain, brain stem, the spinal cord, and the

peripheral nerves, including but not limited to multiple sclerosis, optic neuritis, cerebral sclerosis, post-infectious encephalomyelitis, and epilepsy and associated symptoms.

5 86. The use of claim 85, wherein the disease or disorder is multiple sclerosis, sensory ataxus, neurodegenerative spinocerebellar disorders, hereditary ataxis, cerebellar atrophies, and alcoholism.

10 87. The use of claim 77, wherein the nervous system disorder, disease, or damage involves the retina, photoreceptors, and associated nerves including but not limited to retinitis pigmentosa, macular degeneration, glaucoma, diabetic retinopathy, and associated symptoms.

15 88. The use of claim 77, wherein the nervous system disorder, disease, or damage involves the sensory epithelium and associated ganglia of the vestibuloacoustic complex including but not limited to noise-induced hearing loss, deafness, tinnitus, otitis, labyrinthitis, hereditary and cochleovestibular atrophies, Menieres Disease, and associated symptoms.

20 89. A method of treatment of a pathological condition in a subject comprising administering to an individual in need thereof a therapeutically effective amount of:

- i) the polypeptide of any of the claims 1 to 21; or
- ii) the isolated nucleic acid sequence of any of the claims 22 to 50; or
- iii) the expression vector of any of the claims 51 to 55; or
- iv) a composition of host cells according to any of the claims 56 to 62; or
- 25 v) an implantable biocompatible cell device according to any of the claims 65 72; or
- vi) a packaging cell line according to any of the claims 63 to 64.

30 90. The method of claim 89, wherein the pathological condition is an immunological disorder.

35 91. The method of claim 90, wherein the immunological disorder is selected from the group consisting of: infectious diseases, immune deficiencies, cancer, autoimmune disorders including multiple sclerosis, allergic reactions and conditions, and graft-versus-host disease.

92. The method of claim 89, wherein said medicament is for the treatment of a disease, disorder, or damage associated with the nervous system.

5 93. The method of claim 92, wherein said medicament is for the treatment of a disease, disorder, or damage involving injury to the brain, brain stem, the spinal cord, and/or peripheral nerves, including but not limited to conditions such as stroke, traumatic brain injury, spinal cord injury, diffuse axonal injury, epilepsy, neuropathy, peripheral neuropathy and associated pain and other symptoms.

10 94. The method of claim 92, wherein the Nervous System disorder involves degeneration of neurons and their processes in the brain, brain stem, the spinal cord, and/or the peripheral nerves, including but not limited to Parkinson's Disease, Alzheimer's Disease, senile dementia, Huntington's Disease, amyotrophic lateral sclerosis, neuronal injury associated with multiple sclerosis, and associated symptoms.

15 95. The method of claim 94, wherein the neurodegenerative disease is Parkinson' Disease.

96. The method of claim 94, wherein the neurodegenerative disease is Huntington's Disease.

20 97. The method of claim 94, wherein the neurodegenerative disease is amyotrophic lateral sclerosis.

25 98. The method of claim 92, wherein the nervous system disorder is a disease, disorder, or damage involving dysfunction and/or loss of neurons in the brain, brain stem, the spinal cord, and/or peripheral nerves, including but not limited to conditions caused by metabolic diseases, nutritritional deficiency, toxic injury, malignancy, and/or genetic or idiopathic conditions including but not limited to diabetes, renal dysfunction, alcoholism, chemotherapy, chemical agents, drug abuse, vitamin deficiency, and infection.

30 99. The method of claim 98, wherein the disease is peripheral neuropathy and associated pain.

35 100. The method of claim 92, wherein the nervous system disorder is a disease, disorder, or damage involving degeneration or sclerosis of glia such as oligodendrocytes, astrocytes and Schwann cells in the brain, brain stem, the spinal cord, and the peripheral nerves, including but not limited to multiple sclerosis, optic

neuritis, cerebral sclerosis, post-infectious encephalomyelitis, and epilepsy and associated symptoms.

5 101. The method of claim 100, wherein the disease or disorder is multiple sclerosis, sensory ataxus, neurodegenerative spinocerebellar disorders, hereditary ataxia, cerebellar atrophies, and alcoholism.

10 102. The method of claim 92, wherein the nervous system disorder, disease, or damage involves the retina, photoreceptors, and associated nerves including but not limited to retinitis pigmentosa, macular degeneration, glaucoma, diabetic retinopathy, and associated symptoms.

15 103. The method of claim 92, wherein the nervous system disorder, disease, or damage involves the sensory epithelium and associated ganglia of the vestibuloacoustic complex including but not limited to noise-induced hearing loss, deafness, tinnitus, otitis, labyrinthitis, hereditary and cochleovestibular atrophies, Menieres Disease, and associated symptoms.

20 104. The method of claim 89, wherein the subject is a human being.

105. A method of preventing apoptosis in a mammalian neuronal cell, said method comprising exposing said neuronal cell to a polypeptide as defined in any of the claims 1 to 21.

25 106. A method of enhancing survival of a mammalian neuronal cell, said method comprising exposing said neuronal cell to a polypeptide according to any of the claims 1 to 21.

30 107. A method of generating a neuron, said method comprising exposing a neuronal precursor cell or a neuronal stem cell to a polypeptide according to any of the claims 1 to 21.

35 108. A method of expanding a composition of mammalian cells, comprising administering to said composition the polypeptide of any of the claims 1 to 21; or transducing/transfecting the cells with the expression vector of any of the claims 51 to 55.

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109. A method of differentiating a composition of mammalian cells, comprising administering to said composition the polypeptide of any of the claims 1 to 21; or transducing/transfecting the cells with the expression vector of any of the claims 51 to 55.

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110. An antibody capable of binding to a polypeptide of any of the claims 1 to 21.

111. The antibody of claim 110, being selected from the group consisting of: polyclonal antibodies, monoclonal antibodies, humanised antibodies, single chain antibodies, recombinant antibodies.

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112. An immunoconjugate comprising the antibody of claim 110 and a conjugate selected from the group consisting of: a cytotoxic agent such as a chemotherapeutic agent, a toxin, or a radioactive isotope; a member of a specific binding pair, such as avidin or streptavidin or an antigen; an enzyme capable of producing a detectable product.

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113. An isolated polypeptide selected from the group consisting of AA₁₂₈-AA₂₉₃ of SEQ ID No 3, AA₁₂₁-AA₂₉₃ of SEQ ID No 3, AA₁₂₉-AA₂₉₄ of SEQ ID No 8, AA₁₂₂-AA₂₉₄ of SEQ ID No 8, AA₁₂₆-AA₂₉₁ of SEQ ID No 13, AA₁₁₉-AA₂₉₁ of SEQ ID No 13, and variant of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 15 of the amino acid residues in the sequence are so changed.

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114. The isolated polypeptide of claim 113, wherein the changed amino acids are selected from those designated as unconserved, weakly conserved or strongly conserved in Figure 3a.

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115. An isolated polypeptide selected from the group consisting of SEQ ID No 19, 20, 21, 22, 23, and 24, and variant of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 15 of the amino acid residues in the sequence are so changed.

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116. The isolated polypeptide of claim 115, wherein the changed amino acids are selected from those designated as unconserved, weakly conserved or strongly conserved in Figure 3a.

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117. An isolated polypeptide selected from the group consisting of:

- i) AA₃₀-AA₂₈₈ of SEQ ID No 3, and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₅-AA₂₉₃ of SEQ ID No 3;
- 5 ii) AA₂₈-AA₂₈₆ of SEQ ID No 13 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₃-AA₂₉₁ of SEQ ID No 13;
- 10 iii) AA₃₁-AA₂₈₉ of SEQ ID No 8 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₆-AA₂₉₄ of SEQ ID No 8; and
- iv) variants of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 20 of the amino acid residues in the sequence are so changed.

118. An isolated polypeptide selected from the group consisting of:

- i) AA₁₇₁-AA₂₈₈ of SEQ ID No 3, and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₁₆₅-AA₂₈₈ of SEQ ID No 3;
- 20 ii) AA₁₆₉-AA₂₈₆ of SEQ ID No 13 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₁₆₄-AA₂₉₁ of SEQ ID No 13;
- iii) AA₁₇₂-AA₂₈₉ of SEQ ID No 8 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, i.e. up to AA₁₆₇-AA₂₉₄ of SEQ ID No 8;
- 25 iv) variants of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 10 of the amino acid residues in the sequence are so changed.

119. An isolated polypeptide selected from the group consisting of:

- 30 i) AA₃₀-AA₁₁₈ of SEQ ID No 3, and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₅-AA₁₂₃ of SEQ ID No 3;
- ii) AA₂₈-AA₁₁₆ of SEQ ID No 13 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₃-AA₁₂₁ of SEQ ID No 13;
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- iii) AA₃₁-AA₁₁₉ of SEQ ID No 8 and polypeptides having from one to five extra amino acids from the native sequence in one or both ends, up to AA₂₆-AA₁₂₄ of SEQ ID No 8; and
- iv) variants of said polypeptides, wherein any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 10 of the amino acid residues in the sequence are so changed.

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120. The polypeptide of claim 117, 118, or 119, wherein the changed amino acids are selected from those designated as unconserved, weakly conserved or strongly conserved in Figure 3a.

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121. An isolated polynucleotide coding for a polypeptide according to any of claims 113 to 119.